REMARKS

A. Status of the Claims

Claims 1-4, 6-9, 15-31, 33-37, and 39-40 are currently pending. By virtue of the present amendment, claim 1 has been amended to recite "and wherein at least 90% by weight of the apomorphine has an aerodynamic diameter of not more than 10 μm". Support for this amendment can be found e.g. on page 64 of the corresponding PCT publication at lines 3-5.

It is submitted that no new matter has been added by virtue of this amendment.

B. Rejection under § 103(a)

Claims 1-4, 6-9, 15-31, 33-37, and 39-40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Edwards et al. (US 2002/0035993) in view of 1993 Drug Information Handbook (Lacy, C. et al., Lexi-Comp, Inc: Cleveland, 1993, pp 506-507) ("DIH"), Gupta et al. (US 2002/0006933), Merkus (U.S. Patent No. 5,942,251) and Keller et al. (U.S. Patent No. 6,645,466).

As presently amended, independent claim 1 recites:

> A passive dry powder inhaler device containing a dry powder formulation comprising apomorphine and a metal stearate, wherein upon actuation of the device, a dosing efficiency at 5μm of at least 70% is achieved and wherein at least 90% by weight of the apomorphine has an aerodynamic diameter of not more than 10 μm.

In other words, the claimed invention is directed to dosing efficiency at 5 μm of at least 70% by using a metal stearate, such as magnesium stearate, in a dry powder formulation delivered by a passive dry powder inhaler device. As defined in the PCT Publication at page 2, lines 11-14, "dose efficiency" is the amount of the dose of the pharmaceutical dry powder formulation which, upon being dispensed from the delivery device, is below a specific aerodynamic particle size.

As described on page 64 of the PCT publication, the fine particles of the presently claimed invention – which as specified in amended claim 1 have a mass median aerodynamic diameter ("MMAD") of less than 10 μm -- are thermodynamically unstable due to their high surface area to volume ratio, which provides significant excess surface free energy and encourages particles to agglomerate. This agglomeration is due, in part, to the size of the particles. The predominant forces acting on these particles are gravity and intraparticulate forces. Due to their small size and mass, gravity is no longer the predominant force acting on these particles but instead intraparticulate forces tend to predominate. The tendency to agglomerate means that fine particle fraction ("FPF") is unpredictable. The inventors of the present application have shown that the addition of magnesium stearate consistently achieves an FPF of over 70% in passive dry powder inhaler devices. An example of this is found in the tables on pages 146 and 148 of the PCT publication.

It is respectfully submitted that the prior art references cited by the Examiner do not achieve this claimed dose efficiency and that none of these prior art references suggests that this dose efficiency can be achieved through the use of metal stearates.

To support his rejection, the Examiner cited to the Edwards reference (US 2002/ 0035993) for disclosing inter alia the use of carrier particle in respirable compositions and a delivery of at least about 50% of the mass of the particles (abstract). Further, the Examiner asserts on page 5, paragraph 2 of the office action that the efficiencies of the Edwards reference are overlapping to that of the present claims. However, the Edwards reference does not teach or suggest that the "mass of particles" needs to be of any specific aerodynamic particle size. Edwards merely states that at least 50% of the mass of the particles are delivered to the respiratory tract, which is defined in paragraph 0002 as encompassing the upper airways, including the oropharynx and larynx, followed by the lower airways, which include the trachea followed by bifurcations into the bronchi and bronchioli. Therefore, delivery to the respiratory tract in the Edwards reference could involve delivering just to the oropharynx and larynx. Moreover, up to 50% of the mass of the particles may stay in the device. In view of this teaching, one of skill in the art would clearly understand that the Edwards reference does not

meet the requirements of claim 1 of "a dosing efficiency at 5μm of at least 70% is achieved and wherein at least 90% by weight of the apomorphine has an aerodynamic diameter of not more than 10 μm".

In the Office Action, the Examiner also refers to paragraphs [0018] to [0021] of the Edwards reference. However, these paragraphs are directed to inclusion of carrier having a particular tap density. Further, although paragraph [0022] of the Edwards reference does discuss mass median geometric diameter (MMGD) and mass median aerodynamic diameter (MMAD) of the carrier particles, this disclosure does not relate to dosing efficiency of a dry powder composition as required by the claims of this application.

In fact, paragraph [0021] of the Edwards reference purportedly teaches that the energy holding the particles of the dry powder in an aggregated state is such that a patient's breath, over a reasonable physiological range of inhalation flow rates, is sufficient to deaggregate the powder contained in the receptacle into respirable fractions. The deaggregated particles can penetrate via the patient's breath into and deposit in the airways and/ or deep lung. Therefore, the Edwards reference gives the skilled person no reason to explore modifications to the dry powder composition to tackle agglomeration.

As a result, apart from a general teaching regarding dry powder inhalers and compositions, Edwards does not teach or suggest any of the specific features of claim 1 and should not be considered as relevant prior art against claim 1 as amended. Particularly, Edwards does not provide any indication that a dry powder formulation comprising apomorphine and magnesium stearate can achieve a dosing efficiency at 5 μm of at least 70% upon actuation of the passive device.

In addition to the Edwards reference, the Examiner relies on two further documents (DIH and Gupta et al) for their purported teachings that L-Dopa and apomorphine are known to be suitable for treatment of Parkinson's disease. The Examiner asserts that by virtue of these teachings, a skilled person would be motivated to substitute L-Dopa with apomorphine. The Examiner then cherry picks from the purported teachings of a fourth reference (Merkus) and a

fifth reference (Keller) to formulate the proposition that a skilled person would include magnesium stearate in such a modified formulation because the skilled person would understand from the Merkus reference that apomorphine is unstable in the presence of water and would understand from the Keller reference that magnesium stearate improves resistance of water sensitive active agents in dry powder formulations.

It is only through reliance on impermissible hindsight that the Examiner is able to reconstruct the present invention. The Examiner picks specific teachings from 4 references to be added to his primary reference Edwards, but provides no motivation for why one of skill in the art would have combined these references to formulate a dry powder composition comprising apomorphine and a metal stearate having the dosing efficiency of the present claims. As explained above, the Edwards reference does not identify a problem with the L-Dopa composition such that one of skill in the art would consider modifications. Further, L-Dopa is one of the several active agents tested in Edwards. A disclosure in a prior art reference that L-Dopa and apomorphine are both possible treatments for the same disease does not provide adequate motivation for one of skill in the art to substitute one of these compounds for the other, particularly because one of skill in the art would be aware that they are very different chemical compounds.

It is respectfully submitted that only in view of the teachings of the present application would one of ordinary skill in the art be motivated to formulate a passive dry powder inhaler device containing the dry powder formulation of the present claims.

Further, even if the references were properly combinable, the Examiner is improperly picking and choosing a specific element of from each of the DIH, Gupta, Merkus and Keller references for combination with the Edwards reference. One "...cannot pick and chose among the individual elements of assorted prior art references to recreate the claimed invention." Smith Kline Diagnostics, Inc. v. Helena Laboratories Corporation, 859 F. 2d 878, 887 (Fed. Cir. 1988).

Morever, it is respectfully submitted that none of the additional cited references cure the deficiencies of the Edwards reference in that they do not disclose or suggest "a dosing efficiency

at 5μm of at least 70% is achieved and wherein at least 90% by weight of the apomorphine has an aerodynamic diameter of not more than 10 μm" and therefore, a combination of all five of the cited documents cannot lead to all the recited features of claim 1.

The Gupta reference (U.S. 2002/ 0006933) is a disclosure regarding purported use of apomorphine in the treatment of Parkinson's. It provides no disclosure regarding specific formulation of apomorphine for increasing dosing efficiency.

The Examiner refers to column 4, lines 16 and 17 of the Merkus reference (U.S. 5942251) for the purported teaching that apomorphine is sensitive to moisture. However, these lines refer to the instability of apomorphine in aqueous solutions and the same column then goes on to refer to several documents which disclose stable dry powder composition containing apomorphine including lactose and water soluble alkaline stabilizers. Therefore, one of skill in the art would look to these stabilizing ingredients and not to a metal stearate when looking to achieve a stable composition of apomorphine. Furthermore, the Merkus reference is concerned with intranasal delivery wherein the powders can be administered using a nasal insufflator (Column 2, line 49) and not a pulmonary delivery. The particle sizes of disclosed in the Merkus reference are less than 100 microns in diameter, preferably between 50 and 100 microns in diameter (Column 2, line 46-47) and not wherein at least 90% of the particles by weight have an aerodynamic diameter of more than 10 μm.

The Keller reference (U.S. 6645466) discusses the purported use of magnesium stearate to improve resistance of active compounds to moisture to improve storage properties of inhalation powders. However, this document provides no evidence that inclusion of magnesium stearate provides an improved dosing efficiency upon actuation of a passive dry powder inhaler device. The only disclosure seems to relate to maintenance of FPF upon storage rather than improvement in dosing efficiency. In fact, Table 6 of the Keller reference appears to show the highest FPF as 43.5%, which is much lower than that the dose efficiency required in claim 1 of the present application.

Hence, the prior art does not provide any indication of the claimed invention. The combination of 5 documents to allege obviousness is in itself an indication of inventiveness, particularly when as in this case, even this combination would not lead the skilled person to the claimed invention.

In view of the above, it is respectfully requested that the § 103(a) rejection of claim 1 based on Edwards et al. (US 2002/0035993) in view of 1993 Drug Information Handbook (Lacy, C. et al., Lexi-Comp, Inc: Cleveland, 1993, pp 506-507) ("DIH"), Gupta et al. (US 2002/0006933), Merkus (U.S. Patent No. 5,942,251) and Keller et al. (U.S. Patent No. 6,645,466) be removed. As claims 2-4, 6-9, 15-31, 33-37, and 39-40 depend from claim 1, it is respectfully requested that for the same reason, the rejection of these claims also be removed.

C. Rejection under § 103(a)

Claim 14 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Edwards et al. (US 2002/0035993) in view of the 1993 Drug Information Handbook (Lacy, C. et al., Lexi-Comp, Inc.: Cleveland, 1993, pp 506-507) ("DIH"), Gupta et al. (US 2002/0006933), Merkus (U.S. Patent No. 5,942,251) and Keller et al. (U.S. Patent No. 6,645,466) as applied to claims 1-4, 6-9, 15-31, 33-37, 39-40 above, and further in view of Licalsi et al. (U.S. Patent No. 6,651,655).

Claim 14 depends from claim 1 and recites: "A device as claimed in claim 1, wherein the dry powder formulation is in pre-metered doses stored in one or more foil blisters."

The Examiner's rejection of claim 14 differs from that of the other claims in that it adds a sixth reference, Licalsi et al (U.S. 6,651,655) for the purported teaching that foil blisters are conventionally used in the art to contain pre-metered inhalable dry powder formulations for use with a dry powder inhaler. As with the other 4 references combined with the Edwards reference, the Licalsi reference is picked for its teaching of a particular element, without provision by the Examiner of a motivation for it to be combined with the Edward reference or any of the other 4 cited references. It is respectfully submitted that cherry picking a claim element in this manner to achieve the formulation of claim 14 involves the use of impermissible hindsight. It is further

submitted that even if the six references were properly combinable, the Examiner is improperly picking and choosing a specific element of from each of the DIH, Gupta, Merkus, Keller and Licasi references for combination with the Edwards reference. One "...cannot pick and chose among the individual elements of assorted prior art references to recreate the claimed invention." Smith Kline Diagnostics, Inc. v. Helena Laboratories Corporation, 859 F. 2d 878, 887 (Fed. Cir. 1988).

Further, and as explained above for the 4 references combined with the Edwards rejection, the additional cited references – including the Licasi reference – do not cure the deficiencies of the Edwards reference in that they do not disclose or suggest "a dosing efficiency at 5μm of at least 70% is achieved and wherein at least 90% by weight of the apomorphine has an aerodynamic diameter of not more than 10 μm" and therefore, a combination of all six of the cited documents cannot lead to all the recited features of claim 1.

The Licalsi patent is purportedly directed to a method for creating an immune response in a patient wherein a vaccine material is prepared as a vaccine formulation including dry powder vaccine particles and the formulation is inhaled. The Licalsi formulation does not disclose or suggest a dosing efficiency, nor does it teach or suggest the use of apomorphine or a metal stearate. Therefore, the Licalsi patent cannot cure the deficiencies of the Edwards in view of 1993 Drug Information Handbook, Gupta et al., Merkus and Keller et al.

It is therefore respectfully requested that this rejection be removed

D. Non Statutory Double Patenting

Claims 1-4 and 19-32 were provisionally rejected on the ground of nonstatutory obviouness-type double patenting as being unpatentable over claims 1, 21, 24, 26, 42 and 44 of copending Application No. 10/552,231 and also over claims 1 and 99-100 of copending Application No. 12/459,686 in view of Staniforth et al. (US 2004/0204439).

In response, Applicants respectfully submit that the filing of a terminal disclaimer will be considered upon notification that the pending claims are otherwise allowable.

Conclusion

This Response is being submitted in response to the Office Action dated October 13, 2010 in the above-identified application. Concurrently with this Response, Applicant submits a petition for a two-month extension of time for filing a response, along with the requisite fee. If it is determined that any additional fee is due in connection with this filing, the Commissioner is authorized to charge said fees to Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly requested.

Respectfully submitted,

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